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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

EXTERNAL

: Shirai, et al. Applicant

App. No : 10/521,958

Filed

: January 21, 2005

For

: INDOMETHACIN

PREPARATION

Examiner : Jean-Louis, Samira

Art Unit

Conf No. : 2101

: 1617

2nd DECLARATION OF MAKOTO KANEBAKO AND HITOMI CHIBA UNDER 37 C.F.R. § 1.132

Commissioner for Patents P.O. Box 1450

Alexandria, VA 22313-1450

Dear Sir:

We, Makoto Kanebako and Hitomi Chiba, declare as follows

- 1. We are researchers in KOWA Company Fuji Research Laboratory. We are familiar with the Office Actions, cited references and claims of the above-referenced application.
- 2. In order to establish the criticality of a melting point temperature of 40°C or higher, the following experiments were performed. Gel-cream formulations were prepared as described in U.S. Application No. 10/521,958 for Example Formulations 1-3 and Reference Formulations 1-8. See Table 1 (attached).
- 3. Example Components Glyceryl monostearate, Sorbitan monostearate and Stearyl alcohol having a melting point of 40°C or higher were compared to analogs having a melting point of less than 40°C. The Example and Reference Components are shown in Table 2 (attached).

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- 4. Example 1 and References 1 and 2 relate to glycerin fatty acid ester. As shown in Table 2, Glyceryl monostearate has a melting point higher than 40°C, but Reference Components 1 and 2, Glyceryl undecylenate and Glyceryl isostearate have melting points under 40°C. In the case of Glyceryl undecylenate, the melting point is 36°C, just under 40°C. Referring to Table 1, there is no phase separation for Glyceryl monostearate even at one month, whereas phase separation in the two Reference Components is observed at 2 weeks. We conclude that within the genera of glyceryl fatty acid esters, only species having a melting point of 40°C or higher (such as Glyceryl monostearate) can be stored without phase separation in a gel-cream formulation.
- 5. Example 2 and References 3, 4, and 5 relate to Sorbitan fatty acid ester. As shown in Table 2, Sorbitan monostearate has a melting point of 40°C or higher. Sorbitan monostearate was compared to three analogs. Sorbitan monoisostearate and Sorbitan monooleate both have the same number of carbon atoms as Sorbitan monostearate (18) but lower melting points. Sorbitan monolaurate has 12 carbons. As shown by the Data of Table 1, there is no phase separation for Sorbitan monostearate having a melting point of 40°C or higher at one month storage. In contrast, Reference Components 3 and 5 showed phase separation at 2 weeks and Reference Component 4 showed phase separation at one month. We conclude that gel-cream formulations which include Sorbitan fatty acid esters with a melting point of 40°C or higher can be stored without phase separation while analogs having a melting point below 40°C cannot be stored without phase separation.
- 6. Example 3 and References 6, 7, and 8 relate to fatty alcohol. As shown in Table 2, Stearyl alcohol has a melting point of 40°C or higher. The Reference Components, Octyl alcohol, Decyl alcohol and Lauryl alcohol, all have melting points below 40°C. As shown in Table 1, gelcreams formulated with Stearyl alcohol do not show phase separation at one month while the formulations using the fatty alcohols having lower melting points were not even stable initially. We conclude that fatty alcohols having a melting point of 40°C or higher are effective in gelcream formulations to prevent separation upon storage whereas fatty alcohols having a melting point below 40°C are not effective.

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- 7. The stabilizing effect of surfactants having a melting point of 40°C or higher in gel-cream formulations and the criticality of the higher melting point could not have been predicted based upon the disclosures of Kimura (JP 10-182458) and Inagi (US 4309414).
- 8. We declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States codes and that such willful, false statements may jeopardize the validity of the application or patent issuing therefrom.

Dated: November 18, 2008

Dated: November 14, 2008

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unit: (%)

					Fo	Formulation	c				
Component	Example 1	Example 2	Example 3	Reference 1	Reference Reference Reference Reference Reference Reference Reference Reference	Reference 3	Reference	Reference 5	Reference 6	Reference 7	Reference 8
Indomethacin	7	1	7		7	-	-	1	1	ï	
Octvldodecvl Myristate	5	2	5	2	2	S	s	2	s	2	2
Diisopropyl Adipate	5	5	S	2	2	'n	5	2	S.	s	rs.
	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Hydroxypropyl-Methylcellulose 2910	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
L-menthol	3	9	9	٣	3	3	3	3	3	m	e
Polyethylene glycol 400	1	ď	1	ı	-	-	1	ľ	1		1
Isopropanol	36	36	36	36	36	. 36	36	36	36	36	36
EDTA-2Na	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Sodium bisulfite	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	90.0
Diisopropanolamine	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
Water	44.2	45.7	44.2	44.2	44.2	45.7	45.7	45.7	44.2	44.2	44.2
Glyceryl monostearate (C18)	2	1		-		,	ı	-	,	-	,
Sorbitan monostearate (C18)	,	0.5		ı	,	1	,	-	,		
Stearyl alcohol (C18)			2		1	,	,	,	ı	1	1
Glycervl undecylenate (C10)	-	,		2	,	,	ļ	-	-	-	,
Glyceryl isostearate (C18)		,	'	,	2		1		,	1	
Sorbitan monolaurate (C12)	,	,	,	,	,	0.5			,	,	,
Sorbitan monoisostearate (C18)	'	,	1		-	1	0.5		1	1	1
Sorbitan monooleate (C18)	-	1	1		-			0.5		1	ı
Octv1 alcohol (C8)	,	-	1		-	-		-	2		,
Decv1 alcohol (C10)	1	ı	-	,	-	1			1	23	ı
Lauryl alcohol (C12)	ľ	'	1	1	-	-	1	1	1	,	2
Melting point of surfactant (°C)	54-58	55-59	26-58	36	below25	13-14	below25	-10	-15	7	24-27
Initial	0	0	0	0	0	o	0	0	×	×	×
separation Stored for 2 week (5°C)	0	0	0	×	×	×	0	×	×	×	×
stability stored for 1 month (5°C)	0	0	0	×	×	×	×	×	×	×	×
Criteria for evaluation	<o; pha<="" td=""><td>ise separ</td><td>ation wa ation wa</td><td><o; not="" observed="" phase="" separation="" was=""> <x; observed="" phase="" separation="" was=""></x;></o;></td><td>served></td><td></td><td></td><td></td><td></td><td></td><td></td></o;>	ise separ	ation wa ation wa	<o; not="" observed="" phase="" separation="" was=""> <x; observed="" phase="" separation="" was=""></x;></o;>	served>						
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Table 2 Deta

Detail description of surfactant

	Component	Commercial product	Melting point	Length of carbon chain
Example 1	Glyceryl monostearate	NIKKOL MGS-F20	54~58°C	218
Reference 1	Glyceryl undecylenate	NIKKOL MGU	36°C	C10. unestureted fatt:
Reference 2	Reference 2 Glyceryl isostearate	NIKKOL MGIS	below 25°C	Cla branched fatter age
Example 2	Sorbitan monostearate	NIKKOL SS-10M		בין ביים ביים ביים מכזת
Reference 3	Reference 3 Sorbitan monolaurate	RHEODOL SP-L10	13~14°C	012
Reference 4	Reference 4 Sorbitan monoisostearate NIKKOL SI-10RV	NIKKOL SI-10RV	ړ	and a bodonest a la
Reference 5	Reference 5 Sorbitan monooleate	RHEODOL SP-010V	Т	C10 mermined racky acid
Example 3	Stearyl alcohol	NIKKOL Stearyl alcohol	သို့င	C18
Reference 6	Reference 6 Octyl alcohol			33
Reference 7	Reference 7 Decyl alcohol	KALCOL1098	1,0	C10
Reference 8	Reference 8 Lauryl alcohol	KALCOL2098	24~27%	513